PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	§	
Rajindra Aneja	§	Group Art Unit: 1626
	§	
Serial No.: Unknown	§	
Filed: April 3, 2001	§	Examiner: Ambrose, M.G.
	§	
Prior Serial No.: 08/872,222	§	
Prior Filing Date: June 10, 1997	§	Atty. Dkt.: 4020.000499
	§	
For: MOLECULAR PROBES AND MODULATORS FOR PI-PLC AND PI 3 KINASE	§	

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Rhonda Fairchild

Rhonda Fairchild

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, the Examiner is respectfully requested to enter the following amendments. Remarks supporting patentability of all claims are also included, which the Examiner is respectfully requested to consider. All claims are believed to be condition for allowance, and examination and consideration is respectfully requested on this basis.

AMENDMENT

In the Specification:

Please replace the entire specification from the parent application, other than the claims, with the enclosed substitute specification.

In the Claims:

The accompanying paper requests cancellation of all pending claims except claim 1, without prejudice or disclaimer.

Please further cancel claim 1, after according a filing date to this application.

Please add new claims 11-53, as follows:

11. A phosphoinositide analogue based on di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol having at least one additional hydroxyl group derivatized as a phosphate, wherein said phosphoinositide analogue incorporates one or more of the following modifying structural features:

(a) the 2-OH is rendered non-nucleophilic by derivatization or replacement; or

(b) a reporter group or conjugand is incorporated in the fatty acyl or inositol residue;

wherein the core structure and absolute stereochemistry of the unmodified di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol phosphate or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol phosphate is maintained in said phosphoinositide analogue.

12. The phosphoinositide analogue of claim 11, wherein said phosphoinositide analogue is a phosphoinositide-(mono-phosphate) analogue.

13. The phosphoinositide analogue of claim 11, wherein said phosphoinositide analogue is a phosphoinositide-(di-phosphate) analogue.

14. The phosphoinositide analogue of claim 13, wherein said phosphoinositide analogue is a PtdIns(4,5)P_2 analogue.

15. The phosphoinositide analogue of claim 11, wherein said phosphoinositide analogue is a phosphoinositide-(poly-phosphate) analogue.

16. The phosphoinositide analogue of claim 11, wherein the 2-OH is rendered non-nucleophilic by derivatization or replacement.

17. The phosphoinositide analogue of claim 16, wherein the 2-OH is rendered non-nucleophilic by derivatization.

18. The phosphoinositide analogue of claim 17, wherein the 2-OH is rendered non-nucleophilic by derivatization to form a 2-OCOR or 2-OR phosphoinositide analogue, wherein R is alkyl, substituted alkyl or alkenyl.

19. The phosphoinositide analogue of claim 18, wherein the 2-OH is rendered non-nucleophilic by derivatization to form 2-*O*Ac.

20. The phosphoinositide analogue of claim 18, wherein the 2-OH is rendered non-nucleophilic by derivatization to form a 2-OCOR or 2-OR phosphoinositide analogue, wherein R is CH_3.

21. The phosphoinositide analogue of claim 18, wherein the 2-OH is rendered non-nucleophilic by derivatization to form a 2-OCOR or 2-OR phosphoinositide analogue, wherein R is ω-amino-alkyl.

22. The phosphoinositide analogue of claim 18, wherein the 2-OH is rendered non-nucleophilic by derivatization to form a 2-OCOR or 2-OR phosphoinositide analogue, wherein R is N-substituted-ω-amino-alkyl.

23. The phosphoinositide analogue of claim 18, wherein the 2-OH is rendered non-nucleophilic by derivatization to form a 2-OCOR or 2-OR phosphoinositide analogue, wherein R is N,N-disubstituted-ω-amino-alkyl.

24. The phosphoinositide analogue of claim 16, wherein the 2-OH is rendered non-nucleophilic by replacement.

25. The phosphoinositide analogue of claim 24, wherein the 2-OH is rendered non-nucleophilic by replacement to form the 2-deoxyhalo or 2-dideoxyhalo phosphoinositide analogue.

26. The phosphoinositide analogue of claim 25, wherein the 2-OH is rendered non-nucleophilic by replacement to form the 2-deoxyfluoro phosphoinositide analogue.

27. The phosphoinositide analogue of claim 11, wherein a reporter group or conjugand is incorporated in the fatty acyl or inositol residue.

28. The phosphoinositide analogue of claim 27, wherein a reporter group is incorporated.

29. The phosphoinositide analogue of claim 28, wherein the reporter group is a photoaffinity reporter group.

30. The phosphoinositide analogue of claim 28, wherein the reporter group is a fluorescent reporter group.

31. The phosphoinositide analogue of claim 28, wherein the reporter group is a spin probe reporter group.

32. The phosphoinositide analogue of claim 28, wherein the reporter group is a radioactive label reporter group.

33. The phosphoinositide analogue of claim 28, wherein the reporter group is a stable isotope label reporter group.

34. The phosphoinositide analogue of claim 27, wherein a conjugand is incorporated.

35. The phosphoinositide analogue of claim 34, wherein the conjugand is alkyl-C=O, ω-NH_2-alkyl-C=O, ω-NH_2-alkyl, ω-thio-(alkyl-C=O) or ω-thio-alkyl.

36. The phosphoinositide analogue of claim 34, wherein the conjugand is suitable for linking the phosphoinositide analogue to a polymer.

37. The phosphoinositide analogue of claim 34, wherein the conjugand is suitable for linking the phosphoinositide analogue to a chromatographic matrix.

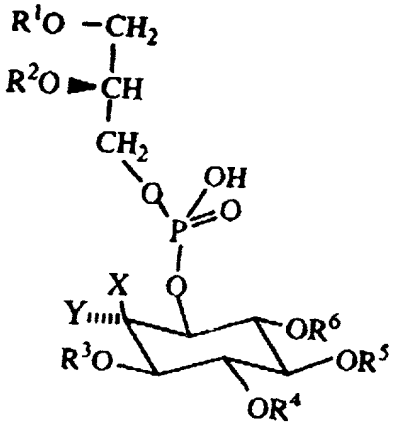
38. The phosphoinositide analogue of claim 34, wherein the conjugand is suitable for linking the phosphoinositide analogue to a gold surface.

39. The phosphoinositide analogue of claim 34, wherein the conjugand is suitable for linking the phosphoinositide analogue to a reporter group.

40. The phosphoinositide analogue of claim 11, wherein one or both glycerol esters are replaced by ether bonds.

41. A selectively *O*-protected phosphoinositide analogue obtained as a phosphodiester intermediate formed by the reaction of a selectively protected *myo*-inositol phosphate or *scyllo*-

inositol phosphate and an *sn*-3-phosphatidic acid or glycero-ether analogue, wherein the said *O*-protected phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is P(=O)(O-protecting group)$_2$,

and wherein:

(a) X = F, Cl, Br, OC(=O)R, OR, or P(=O)(O-protecting group)$_2$, and Y = H; or

X = Y = H; or

(b) X = H, and Y = F, Cl, Br, OC(=O)R, OR, or P(=O)(O-protecting group)$_2$; or

(c) X = Y = F or (=O);

where R = alkyl, especially methyl or ethyl, alkenyl, alkynyl, ω-aminoalkyl, N-substituted-ω-aminoalkyl or N,N-disubstituted-ω-aminoalkyl;

and wherein

(d) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R, R' = alkyl or alkenyl;

and wherein:

(e) R^3 = H, or P(=O)(O-protecting group)$_2$,

(f) R^4 = H, or P(=O)(O-protecting group)$_2$,

(g) R^5 = H, or P(=O)(O-protecting group)$_2$,

(h) R^6 = H, P(=O)(O-protecting group)$_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

42. The phosphoinositide analogue of claim 11, wherein:

(a) the 2-OH is rendered non-nucleophilic by derivatization or replacement; and

(b) a reporter group or conjugand is incorporated in the fatty acyl or inositol residue;

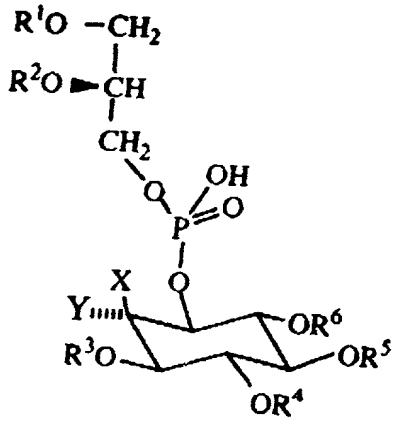
wherein the core structure and absolute stereochemistry of the unmodified di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol phosphate or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol phosphate is maintained in said phosphoinositide analogue.

43. A phosphoinositide analogue based on di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol having at least one additional hydroxyl group derivatized as a phosphate, wherein the 2-OH is rendered non-nucleophilic by derivatization or replacement and wherein the core structure and absolute stereochemistry of the unmodified di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol phosphate or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol phosphate is maintained in said phosphoinositide analogue.

44. The phosphoinositide analogue of claim 11, wherein said phosphoinositide analogue is based on di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol phosphate.

45. The phosphoinositide analogue of claim 11, wherein said phosphoinositide analogue is based on di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol phosphate.

46. A selectively *O*-protected phosphoinositide analogue obtained as a phosphodiester intermediate formed by the reaction of a selectively protected *myo*-inositol phosphate or *scyllo*-inositol phosphate and an *sn*-3-phosphatidic acid or glycero ether analogue, wherein the said *O*-protected phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is P(=O)(O-protecting group)$_2$,

and wherein

(a) X = OH, and Y = H; or X = H, and Y = OH;

and wherein

(b) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R = alkyl, alkenyl, alkynyl, R' = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R'= alkyl, alkenyl, alkynyl, R = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R = R', except when R = R' = alkyl;

and wherein

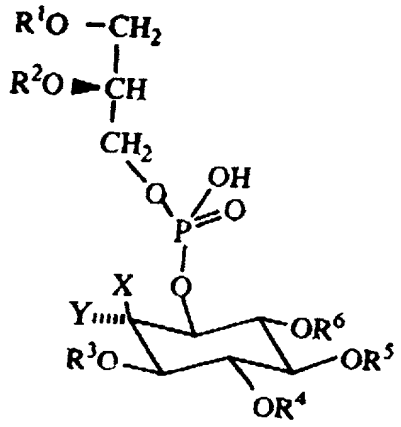
(c) R^3 = H, or P(=O)(O-protecting group)$_2$,

(d) R^4 = H, or P(=O)(O-protecting group)$_2$,

(e) R^5 = H, or P(=O)(O-protecting group)$_2$,

(f) R^6 = H, P(=O)(O-protecting group)$_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

47. A selectively *O*-protected phosphoinositide analogue obtained as a phosphodiester intermediate formed by the reaction of a selectively protected *myo*-inositol phosphate or *scyllo*-inositol phosphate and an *sn*-3-phosphatidic acid or glycero ether analogue, wherein the said *O*-protected phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is $P(=O)(O\text{-protecting group})_2$,

and wherein

(a) X = F, Cl, Br, OC(=O)R, OR, or $P(=O)(O\text{-protecting group})_2$, and Y = H; or

X = Y = H; or

(b) X = H, and Y = F, Cl, Br, OC(=O)R, OR, or $P(=O)(O\text{-protecting group})_2$, or

(c) X = Y = F or (=O);

where R = alkyl, especially methyl or ethyl, alkenyl, alkynyl, ω-aminoalkyl, N-substituted-ω-aminoalkyl or N,N-disubstituted-ω-aminoalkyl;

and wherein

(d) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R = alkyl, alkenyl, alkynyl, R' = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor,

alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R' = alkyl, alkenyl, alkynyl, R = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R = R';

and wherein

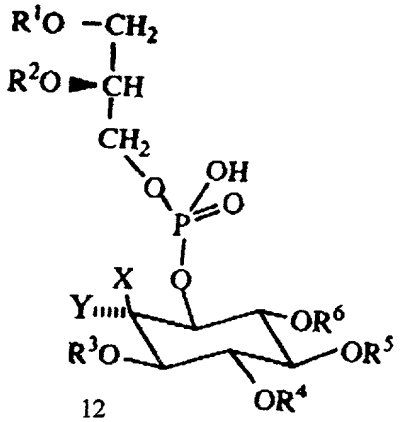
(e) R^3 = H, or P(=O)(O-protecting group)$_2$,

(f) R^4 = H, or P(=O)(O-protecting group)$_2$,

(g) R^5 = H, or P(=O)(O-protecting group)$_2$,

(h) R^6 = H, P(=O)(O-protecting group)$_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

48. A phosphoinositide analogue based on phosphatidylinositolphosphate, wherein the 2-OH is rendered non-nucleophilic by derivatization or replacement or wherein a reporter group or conjugand is incorporated in the fatty acyl or inositol residue; wherein the core structure and absolute stereochemistry of the unmodified phosphatidylinositolphosphate is maintained in said phosphoinositide analogue; and wherein said phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is $P(=O)(OH)_2$,

and wherein

(a) X = F, Cl, Br, OC(=O)R, OR, or $OP(=O)(OH)_2$, and Y = H; or

X = Y = H; or

(b) X = H, and Y = F, Cl, Br, OC(=O)R, OR, or $OP(=O)(OH)_2$; or

(c) X = Y = F or (=O);

where R = alkyl, especially methyl or ethyl, alkenyl, alkynyl, ω-aminoalkyl, N-substituted-ω-aminoalkyl or N,N-disubstituted-ω-aminoalkyl;

and wherein

(d) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R, R' = alkyl or alkenyl;

and wherein

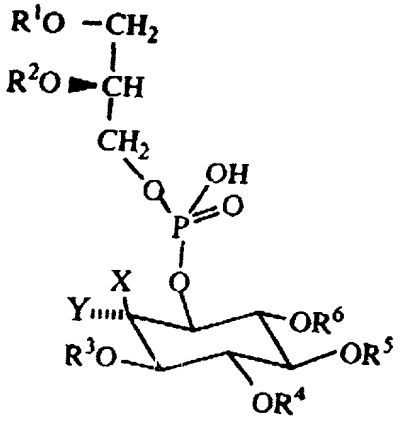
(e) R^3 = H, or $P(=O)(OH)_2$

(f) R^4 = H, or $P(=O)(OH)_2$

(g) R^5 = H, or $P(=O)(OH)_2$

(h) R^6 = H, $P(=O)(OH)_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

49. A phosphoinositide analogue based on phosphatidylinositolphosphate, wherein the 2-OH is rendered non-nucleophilic by derivatization or replacement or wherein a reporter group or conjugand is incorporated in the fatty acyl or inositol residue; wherein the core structure and absolute stereochemistry of the unmodified phosphatidylinositolphosphate is maintained in said phosphoinositide analogue; and wherein said phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is $P(=O)(OH)_2$,

and wherein

(a) X = OH, and Y = H; or X = H, and Y = OH;

and wherein

(b) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R = alkyl, alkenyl, alkynyl, R' = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R' = alkyl, alkenyl, alkynyl, R = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl,

ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R = R', except when R = R' = alkyl;

and wherein

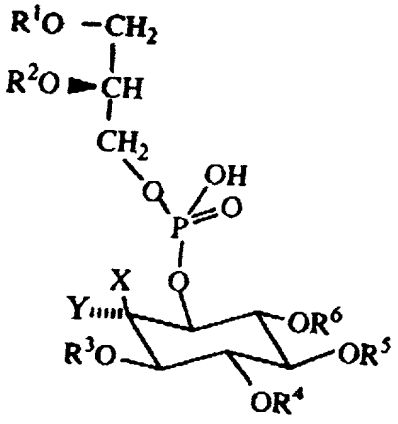
(c) R^3 = H, or $P(=O)(OH)_2$

(d) R^4 = H, or $P(=O)(OH)_2$

(e) R^5 = H, or $P(=O)(OH)_2$

(f) R^6 = H, $P(=O)(OH)_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

50. A phosphoinositide analogue based on phosphatidylinositolphosphate, wherein the 2-OH is rendered non-nucleophilic by derivatization or replacement and a reporter group or conjugand is incorporated in the fatty acyl or inositol residue; wherein the core structure and absolute stereochemistry of the unmodified phosphatidylinositolphosphate is maintained in said phosphoinositide analogue; and wherein said phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is $P(=O)(OH)_2$,

and wherein

(a) X = F, Cl, Br, OC(=O)R, OR, or $OP(=O)(OH)_2$, and Y = H; or

X = Y = H; or

(b) X = H, and Y = F, Cl, Br, OC(=O)R, OR, or $OP(=O)(OH)_2$; or

(c) X = Y = F or (=O);

where R = alkyl, especially methyl or ethyl, alkenyl, alkynyl, ω-aminoalkyl, N-substituted-ω-aminoalkyl or N,N-disubstituted-ω-aminoalkyl;

and wherein

(d) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R = alkyl, alkenyl, alkynyl, R' = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R' = alkyl, alkenyl, alkynyl, R = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, alkyl-fluorophor, hydroxylalkyl, or ketoalkyl; or where R = R';

and wherein

(e) R^3 = H, or $P(=O)(OH)_2$

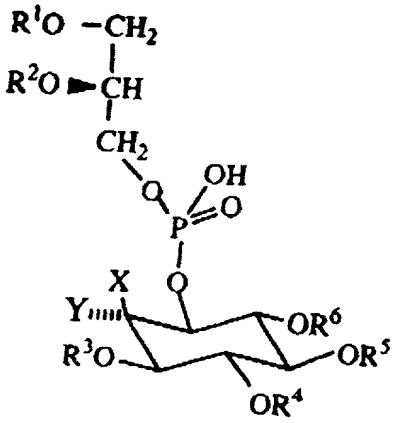
(f) R^4 = H, or $P(=O)(OH)_2$

(g) R^5 = H, or $P(=O)(OH)_2$

(h) R^6 = H, $P(=O)(OH)_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

51. Matched pairs of the 2-modified phosphatidylinositol-phosphates of claim 48 and the corresponding phosphatidylinositol-phosphate structure lacking the 2-modification, wherein X=OH and Y=H, or X=H and Y=OH.

52. The phosphoinositide analogue of claim 11, wherein said phosphoinositide analogue has the structure:



wherein at least one of R^3, R^4, R^5, R^6 is $P(=O)(OH)_2$,

and wherein

(a) X = OH, and Y = H; or X = H, and Y = OH

and wherein

(b) R^1 = RC(=O) or R, R^2 = R'C(=O) or R'

where R = alkyl, alkenyl, alkynyl, R' = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, [alkyl-fluorophor], hydroxylalkyl, or ketoalkyl; or where R' = alkyl, alkenyl, alkynyl, R = ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, ω-(substitutedamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, hydroxylalkyl, or ketoalkyl;

and wherein

(c) R^3 = H, or $P(=O)(OH)_2$

(d) R^4 = H, or $P(=O)(OH)_2$

(e) R^5 = H, or $P(=O)(OH)_2$

(f) R^6 = H, $P(=O)(OH)_2$, ω-aminoalkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, ω-(4-azidosalicylamido)-alkyl, alkyl-aminofluorophor, alkyl-amidofluorophor, or alkyl-fluorophor.

53. A phosphoinositide analogue based on di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol having at least one additional hydroxyl group derivatized as a phosphate, wherein said phosphoinositide analogue incorporates one or more of the following modifying structural features:

(a) the 2-OH is rendered non-nucleophilic by derivatization or replacement; or

(b) a conjugand suitable for linking to a reporter group, polymer, chromatographic matrix, or gold surface is incorporated in the fattyacyl or inositol residue; wherein said conjugand is selected from the group consisting of ω-aminoalkyl, ω-(substitutedamino)-alkyl, ω-aminoalkenyl, ω-sulfhydrylalkyl, ω-carboxyalkyl, hydroxylalkyl and ketoalkyl, and wherein the amino, substitutedamino, sulfhydryl, carboxyl, hydroxyl and keto functions are free and unsubstituted, or are covalently linked to a reporter group;

wherein the core structure and absolute stereochemistry of the unmodified di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol phosphate or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol phosphate is maintained in said phosphoinositide analogue.

REMARKS

I. Continuing Application Status

The present application is a continuation of application Serial No. 08/872,222, filed June 10, 1997 ("the '222 application"; Attorney Docket No. 4020.000400). The inventorship remains the same as the earlier application.

Applicant respectfully requests that the preceding claims and the enclosed substitute specification be entered prior to substantive examination of this application. All of the amendments and additionally presented claims are fully supported by the original parent and earlier provisional applications, to which priority is still properly claimed.

II. Status of the Claims

The accompanying paper requests cancellation of all pending claims except claim 1, without prejudice or disclaimer.

New claims 11-53 have been added, which are fully supported by the original specification and essentially match the non-allowed claims at the end of prosecution of the '222 application. Numbering the present claims starting with claim 11 is believed to be correct, and has the advantage that many of the new claims have the same numbers as those pending at the close of prosecution of the '222 application. Claims 11-53 are therefore in the case.

III. Compliance with 37 C.F.R. § 1.121

Copies of the pending claims are attached hereto as **Exhibit A** and **Exhibit B**. As the present application is a new application, and as all claims are newly presented without actual amendment of former claims, they are believed to be "original claims" for the purposes of this application. Therefore, it is not believed to be necessary under 37 C.F.R. § 1.121(c) to label each claim "(New)", nor to provide a separate exhibit showing the changes to the claims.

Nonetheless, for the convenience of the Examiner, two claim exhibits are provided to show the near-exact correlation of the present claims with those at the close of prosecution of the '222 application. **Exhibit A** therefore includes the notations "Former Claim __" at every point, and includes the notation "Amended as shown", along with underlining where appropriate. **Exhibit B** provides a clean copy of the pending claims in the present application.

In accordance with 37 C.F.R. § 1.121(b)(3), Applicant elects to enter the amendments to the specification in the form of a substitute specification. This is proper under 37 C.F.R. §§ 1.121(b)(3)(i)(ii)(iii), as the present document contains an instruction to replace specification, along with a first substitute specification in clean form and a second substitute specification,

separate from the first substitute specification, marked up to show all changes relative to the previous version of the specification using brackets and underlining.

IV. Additional Support for the Claims

Claims 11-53 are evidently supported by the original specification as they essentially match the claims at the end of prosecution of the '222 application. In particular, new claims 11-40 correspond to former claims 11-40; and new claims 41, 42, 43 and 44-51 correspond to former claims 66, 70, 79 and 84-91, respectively. New claim 52 is an amended version of former claim 81 and new claim 53 is based upon certain preferred aspects of claim 11. Exemplary support for the text of the current claims in the present specification is detailed as follows.

Claim 11 is largely based upon original claim 1 in the '222 application, and also incorporates features of original claim 10 from the '222 application. Earlier alternative and exemplary features in these claims are now recited in dependent claims. Present claim 11 particularly points out and distinctly claims preferred aspects of the overall invention, and includes the changes to claim 11 from the '222 application, as described in detail in the following paragraphs.

Accordingly, claim 11, and all claims dependent thereon, defines the "core structure and absolute stereochemistry" of the unmodified compound as being maintained in the claimed analogue, as supported in the specification at least at page 3, paragraph 3, line 3.

Claim 11, and all claims dependent thereon, also clarifies the claimed phosphoinositide analogues as those analogues based on di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol or di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*scyllo*-inositol having at least one additional hydroxyl group derivatized as a phosphate.

The foregoing language is based on that at page 3 of the Final Action issued in the '222 application, with minor modifications. Specifically, the 1'2' has been omitted from the di-*O*-fattyacyl terminology and *scyllo*-inositol has been added to complement the *myo*-inositol suggested in the Final Action. These features are supported throughout the specification, with exemplary reference to page 6, paragraphs 1, 2 and 3; page 7, paragraphs 2 and 3; page 8, paragraph 1; page 17, paragraph 2; and FIG. 1.

The "wherein" clause of claim 11 unambiguously matches the language recited in the body of the claim, hence the earlier "phosphatidylinositolphosphate" has been replaced with "di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol phosphate" or the *scyllo*-inositol phosphate derivative.

In claims 12 and 15, the phosphoinositide-(mono-phosphate) and phosphoinositide-(poly-phosphate) analogues embody the previous mono and poly options, respectively, within claim 10 in the '222 application.

The phosphoinositide-(di-phosphate) analogues of claim 13 are also supported by original claims 1 and 10 in the '222 application, and the entire specification, with the exact phosphoinositide analogue of claim 14 reflecting that of original claim 1.

Claim 16 reflects feature (i) of original claim 1, with claim 17 defining the derivatization option. Claims 18-23 define different embodiments of derivatization, as originally recited in the alternative within claim 1 in the '222 application. Claim 19 has been revised to correct a typographical oversight. The ω-amino-alkyl and N-substituted-ω-amino-alkyl groups of claims 21-23 have additional support throughout the specification, as exemplified by the structures at the bottom of page 4 of the '222 application.

Claim 24 defines the other feature within part (i) of original claim 1 in the '222 application, namely the replacement strategy. Claims 25 and 26 further exemplify different replacement embodiments, also as recited in original claim 1.

Claim 27 begins feature (ii) of original claim 1 in the '222 application, the reporter group or conjugand aspects of the invention, with claim 28 reciting reporter groups. Claim 27 is a counterpart of claim 16 and has been revised to remove the earlier redundancy. Although claim 27 is drafted in the alternative, it will be understood that, as with claim 11, the claimed subject matter includes modifications wherein a reporter group or conjugand is incorporated in the fatty acyl group and a reporter group or conjugand is incorporated in the inositol residue.

Claims 29-33 separately recite the exemplary reporter groups from original claim 1, with the radioactive and isotopic species being supported by the specification of the '222 application, *e.g.*, at least at page 7, line 26.

Claim 28 recites the other feature of part (ii) from original claim 1 in the '222 application, the conjugands. The conjugands listed within claim 35 are the non-reporter group features exemplified in the structures at the bottom of page 4 of the '222 application. Claims 36-38 relate back to original claim 1, and exemplify various components to which the conjugands may be linked. In addition, the conjugands may provide the linkage to the reporter group, thus conceptually bridging present claims 28-33 and 34-39. Claims 32 and 33 have been revised to correct clerical oversights.

Claim 40 matches former claim 2 in the '222 application.

Present claim 41 matches former claim 66 in the '222 application and captures subject matter encompassed by original claim 8 in the '222 application. As with claim 66 earlier, current claim 41 has been revised to remove the reference to a claim that is no longer pending. The

subject matter of claim 41 has thus been clarified to reflect the approach in former claims 80-82, allowed in the '222 application. In particular, claim 41 has been revised and claims 46 and 47 added so that claims 41, 46 and 47 reflect the precursors to the analogues of allowed claims 80, 81 and 82. Support for claims 41, 46 and 47 exists throughout the specification, particularly at page 7, paragraphs 2, 3, 4 and 5; and page 16, paragraph 3, continuing on page 17.

Present claim 42 matches former claim 70 in the '222 application. The claim is thus based upon claim 11, but has a definite requirement for feature (a) and (b), rather than feature (a) or (b) in the alternative. The language of current claim 42 (former claim 70) has been optimized to match that of claim 11, as described above. Similarly to claims 11 and 27, part (b) of claim 42 is drafted in the alternative and therefore clearly covers phosphoinositide analogues wherein the 2-OH is modified as claimed and a reporter group or conjugand is incorporated in the fatty acyl group, and additionally a reporter group or conjugand is incorporated in the inositol residue.

Claim 43 matches former claim 79 in the '222 application, provided as independent claim to even better correlate with certain preferred aspects of the invention. Present claim 43 is thus also based upon claim 11, but has a definite requirement for feature (a), rather than feature (a) or (b) in the alternative. The language of current claim 43 (former claim 79) has also been optimized to match that of claim 11, as described above.

Claims 44-51 in the present application correspond to former claims 84-91, respectively, in the '222 application, with the following changes.

New claims 46 and 49 are based upon former claims 86 and 89, with two changes. In the last line of part (b) of each claim, before the end of this clause, these claims have been revised to clarify that R may equal R', except when R = R' = alkyl. Also, in part (a) of each of claims 46 and 49, the term "or X = H, and Y = OH" has been added. As claim 11 recites *scyllo*-inositol

based phosphoinositides in addition to *myo*-inositol based structures, the revisions to part (a) of claims 46 and 49 bring these claims into better harmony with claim 11.

Dependent claims 44 and 45 refer to the *myo*-inositol and *scyllo*-inositol of claim 11 in the alternative.

As described above, claims 46 and 47 are counterparts to claim 41 (former claim 66), which together form the precursors for analogues of claims 80, 81 and 82, allowed in the '222 application. Support for claims 46 and 47 exists throughout the specification, particularly at page 6, paragraph 5; page 7, paragraph 2; and in FIG. 2.

Claims 48, 49 and 50 are based upon former claims 88, 89 and 90 in the '222 application and represent allowable claims 80, 81 and 82, redrafted in independent form. As suggested in the Final Action in the '222 application, the language of the base claim and any intervening claims has been used. The improved definitions of R and R' in claims 49 and 50, counterparts to allowed claims 81 and 82, have also been inserted.

Claim 51 is based upon former claims 91 and 83 and is unified with the elected invention and supported by the original specification at page 6, paragraph 2. Claim 51 has been revised to further clarify that the matched pairs comprise the 2-modified phosphatidylinositol-phosphate "and" the corresponding phosphatidylinositol-phosphate structure lacking the 2-modification, and are thus not admixtures. This claim has also been revised to add "or X = H and Y = OH", as supported by claim 11 and discussed above.

New claim 52 represents a sub-set of former claim 81. Former claim 81 was allowed with R^1 and R^2 restricted to R = R′ = certain amino- and related functionalized and substituted alkyl and alkanoyl groups. New claim 52 is directed to other species wherein R and R′ are defined as precise combinations of alkyl, alkenyl and certain amino- and related functionalized

and substituted alkyl and alkanoyl groups. In comparison to former claim 81, new claim 52 has been revised to add "or X=OH, and Y=H" in part (a); to delete "or where R = R'" in the last line of part (b); to delete "alkyl-fluorophor" in each of two occurrences, in lines 5 and 9, of clause (b), whilst properly retaining a third occurrence of alkyl-fluorophor.

Claim 52 has support at various points of the specification, which describes structural types wherein R^1 and R^2 are not identical, exemplified on page 6, paragraph 5 by 1-*O*-hexanoyl-2-*O*-(ω-Cbz-aminobutanoyl)-*sn*-glycero-3-phosphoric acid (**18,** Scheme II, FIG 2), on page 7, paragraph 2 by 1-*O*-hexanoyl-2-*O*-(aminobutanoyl)-*sn*-3-phosphatidyl-based PtdIns(4,5)P_2s, and the derived 4-azidosalicyl photoaffinity-labelled analogue, with corresponding examples on pages 16 and 17. Thus, new claim 52 is properly based on combinations of non-identical R^1 and R^2 for both the *myo*-inositol and the *scyllo*-inositol configurations of the 2-hydroxyl group.

Finally, new claim 53 reflects certain preferred aspects of claim 11, and is supported by claim 11 in the context of the entire specification and claims, *e.g.*, such as by claims 27-39.

It will therefore be understood that no new matter is included within any of the claims submitted as part of the present application.

V. Additional Support for the Specification

The minor amendments to the specification are made to unify the *myo* and *scyllo* terminology in the specification. All such amendments were accepted without question in the '222 application and therefore do not constitute new matter. The precise points of the changes in the substitute specification, made with reference to the text of the '222 application as originally filed, are detailed in **Exhibit C**. Additional reasoning and support for such amendments follows.

As described throughout the specification, the invention of the present and '222 application is applicable to both *myo* and *scyllo* inositol analogues and the replacement reaction

with DAST produces two 2-deoxyfluoro epimers (*myo* and *scyllo*) (notably, see page 6, lines 19-23). During prosecution, Applicant realized that certain of the detailed examples in the specification refer to the *myo* form and certain others to the *scyllo* form, and that unification as *myo/scyllo* was necessary.

The Office will appreciate that the present changes to the specification do not in any way constitute new matter. The Federal Circuit has repeatedly held that a patent discloses not only what is expressly described, but necessarily discloses the characteristics and properties inherent in the described subject matter. *Kennecott Corp. v. Kyocera Int'l Inc.*, 2 U.S.P.Q.2d 1455 (Fed. Cir. 1987). Thus, changes that merely add or correct an explicit description of an inherent characteristic do not introduce new matter into the patent. *Kolmes v. World Fibers Corp.*, 41 U.S.P.Q.2d 1829 (Fed. Cir. 1997). See also, *In re Sulkowski*, 180 U.S.P.Q. 46 (C.C.P.A. 1973); *Ex parte Marsili, Rossetti, and Pasqualucci*, 214 U.S.P.Q. 904, 906 (PTO Bd. App. 1979).

It will therefore be understood that no new matter is included within the substitute specification submitted as part of the present application.

VI. Response to Final Office Action in Parent Application

Certain claims from the '222 application have been allowed. The following reasoning constitutes Applicant's response to the Final and Advisory Actions issued in the '222 application. The response addresses the concerns remaining from the '222 application so that the present claims can be directly progressed to allowance.

A. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 11-40, 66, 70 and 79 in the '222 application, corresponding to claims 11-40, 41, 42 and 43 in the present application, were rejected under 35 U.S.C. § 112, first paragraph as the specification allegedly fails to reasonably provide enabling support for the claimed compounds. Although Applicant respectfully traverses, the concerns in the Final Action are addressed.

The Final Action at pages 3 and 4 assesses the specification as being "enabling for the group of phosphatidylinositols described in claims 80-82" and indicates that "analogues based on 1',2'-di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol having at least one additional hydroxyl group derivatized as a phosphate" would be allowable[1]. Applicants therefore elect to prosecute the indicated allowable subject matter to issuance. Claims 11, 42 and 43 have been revised accordingly, and claim 53 has been added.

In addition to using the Final Action's suggested wording, with minor qualifications to the 1',2'-di-*O*-fattyacyl and *myo*-inositol definitions, as explained below, the present claims address the particular concerns elucidated in the Final Action. The first concern was that the term 'phosphatidylinositolphosphate', when given a broad interpretation, embraced various stereochemical forms of hexahydroxycyclohexane, apparently not supported by the specification. The second concern related to the breadth of the "phosphatidyl-" terminology. Each of these concerns is fully addressed.

As stated in the Final Action, the claims should be given their broadest *reasonable* interpretation, *i.e.*, the broadest *reasonable* interpretation that one of ordinary skill in the art

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[1]The Action bridging pages 3 and 4 particularly refers to analogues of D-*myo*-inositol as being enabled by the disclosure. However, as enabling support is acknowledged for the breadth of claims 80-82, which are not so limited, enabling support has, in fact, been acknowledged for D-*myo*-inositol as well as D-*scyllo*-inositol series of analogues.

would reach *in light of the specification.* Applicant believes that the claims already met this requirement, but in the interest of progressing the application to issuance in a timely and cost effective manner, Applicant elects to use the terminology suggested in the Final Action.

In particular, the term "phosphatidylinositolphosphate", as used in claims 11, 42 and 43 (former claims 11, 70 and 79), and in claim 53, is clearly linked with and qualified by other phrases that adequately and distinctly defined the structure and stereochemistry of the phosphatidylinositolphosphate of the invention. In accordance with such definitions, the term "phosphatidylinositolphosphate" would not be interpreted, by those of skill in the art, in the broad unrestricted sense proposed in the Final Action. Rather, it would be understood to cover a defined range of structural and stereochemical types of phosphatidylinositolphosphates, for which commensurate enabling support is provided in the specification.

The structural and stereochemical type of phosphatidylinositolphosphate and modifications of this structure according to claim 11 (and the other independent claims) were defined and qualified by the phrase: "wherein the core structure and absolute stereochemistry of the unmodified natural phosphatidylinositolphosphate is maintained in said phosphoinositide analogue."

Those of ordinary skill in the art would, in light of the present disclosure, understand that natural phosphatidylinositolphosphates are based on the 1D-1-*myo*-inositol stereostructure and this remains unchanged when modification at C(2)-OH is by direct derivatization. On the other hand, when modification involves substitution of the C(2)-OH, it would be understood that this can result in either retention or inversion of stereochemistry at C-2. Specifically, substitution with inversion of the axial C(2)-OH in the *myo*-series produces analogues with an equatorial C(2)-OH, which are classified and named as derivatives of the 2-equatorial *scyllo*-inositol series.

Modification by incorporating a reporter group or conjugand in accordance with the present invention does not effect the *myo*-inositol or *scyllo*-inositol stereostructure. Modification by incorporating a reporter group or conjugand in accordance with the present invention does not effect the *sn*-glycero-3-phospho stereostructure.

Accordingly, as a skilled artisan would understand, the structures of claim 11 fall into two and only two, stereostructural hexahydroxycyclohexane groups, based respectively on (i) 1D-(*sn*-glycero-3'-phospho)-*myo*-inositol and (ii) 1D-(*sn*-glycero-3'-phospho)-*scyllo*-inositol. These two groups were explicitly illustrated in claims 80-82, allowed in the '222 application. Notwithstanding the enabling support for the claims as written, the language of present claims 11, 42 and 43 (former claims 11, 70 and 79), and claim 53, is chosen to provide an even better correlation with the structural and stereochemical types of phosphatidylinositolphosphates described in the specification and to accord with the specific suggestions in the Final Action.

At page 3, paragraph 2, line 6, the Final Action also raises a concern about the scope of the term "phosphatidyl-" as a part of the "phosphatidylinositolphosphate". This concern is overcome by clarifying the claims to replace phosphatidyl- with "di-*O*-fattyacyl (or alkyl)-*sn*-glycero-3'-phospho-*myo*-inositol" (or *scyllo*-inositol), again using terminology suggested in the Final Action.

The § 112, first paragraph rejections are thus overcome and should be withdrawn.

B. <u>Rejection of Under 35 U.S.C. § 112, First and Second Paragraphs</u>

Claims 11-15, 27-40 and 70 in the '222 application, corresponding to claims 11-15, 27-40 and 42 in the present application, were rejected under 35 U.S.C. § 112, first and second paragraphs, as allegedly not being supported by an enabling specification and as allegedly being

indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention.

Specifically, the Final Action's concern lies with the use of terms such as "photoaffinity, fluorescent, spin and reporter", which are allegedly unsupported in the specification and indefinite when used to describe alternative substituent groups. Although Applicant respectfully traverses, these concerns are also addressed, thus placing current claims 11-15, 27-40, 42 and 53 in condition for allowance.

The Final Action's concern that the specification does not describe "how to use" the compounds of the invention (Final Action at page 4, middle paragraph) generally corresponds to the former rejections based upon a perceived lack of utility and lack of enabling support for "how to use". As summarized in the '222 application prosecution history, such rejections have been withdrawn. In terms of written description as to "how to use" the compounds of the claimed invention, and clarity of expression, the text of the specification at page 7, last paragraph is particularly relevant.

As pointed out in Applicant's second response in the '222 application, it is well established that claims should not be required to be so detailed as to obscure, rather than to particularly point out and distinctly claim the invention. *In re Smythe and Shamos*, 178 USPQ 279, 286 (C.C.P.A. 1973). As terms such as "photoaffinity, fluorescent, spin, reporter and conjugand" are commonly used in the art, they should be accepted as sufficiently definite in the present claims.

Applicant has already provided evidence of the overwhelming use of such terms in the scientific literature, as shown in the exhibits appended to the second response in the '222 application. The Final Action does not comment on the evidence already of record, but merely

reiterates that the claims define the metes and bounds of the invention (Final Action at page 4). The requirement for the claims to perform this function is not in doubt; rather Applicant's position is that there is already significant evidence of record to show that one of ordinary skill in the art would clearly understand the metes and bounds of the invention from the present claims.

The proper test of definiteness is whether, in the light of the teachings of the prior art and of the particular application disclosure, the claims set out and circumscribe, for one possessing an ordinary level of skill in the pertinent art, a particular area with a reasonable degree of particularity. *In re Moore*, 169 USPQ 236 (C.C.P.A. 1971; emphasis added). The literature evidence already of record clearly shows that the questioned claim language would be readily understood by one of ordinary skill in the art when read in light of the specification.

Notwithstanding the evidence of record to date, Applicant now provides additional references to the patent literature to further show that such terms are readily understood in the art. Applicant's search of the U.S. P.T.O. Full Text Database for the period 1999-2000 produced 790 "hits" for the combined terms "(reporter group) or (reporter molecule)". The titles for the first 100 of such issued U.S. patents are provided herewith in **Exhibit D**.

A review of exemplary patent documents reveals that such terms are understood in the art and are perfectly acceptable in U.S. patents. Although many such documents can serve as suitable examples, Applicant provides Hit # 58, Hogan, *et al.*, Nucleic Acid Probes to Ureaplasma, U.S. Patent No. 6,093,538, issued July 25, 2000 ("the '538 patent"; **Exhibit E**).

In summary, the '538 patent uses the phrase "reporter group" 33 times in claims 18-106. In fact, the exact phrase is "one or more **reporter** groups" on all 33 occurrences, which is even broader than "reporter group" (**Exhibit E**). It is noteworthy that none of the claims reciting

"reporter group" is followed by claims that specify a distinct entity as a specific example of "reporter group".

In support of the succinct language in the claims, the '538 patent defines the "reporter group" moiety in the specification as follows:

> "A probe may be labeled with a reporter group moiety such as a radioisotope, a fluorescent or chemiluminescent moiety, or with an enzyme or other ligand which can be used for detection."
>
> U.S. Patent No. 6,093,538 at column 1, lines 37-41.

This information is paraphrased in the '538 patent at column 3, lines 57-60, and further described at column 9, lines 17-48 (**Exhibit E**). No additional information is provided - - simply because no additional information is necessary for those of ordinary skill in the art to understand the metes and bounds of the term "reporter group", as used in the claims.

As the term "reporter group" was accepted as sufficiently definite in the claims of U.S. Patent No. 6,093,538, and 789 other issued U.S. patents (**Exhibit D**), this term must also be accepted as definite in the present application. 35 U.S.C. § 282. The MPEP also clearly indicates that uniform examination standards should be applied, stating "the standards of patentability applied in the examination of claims must be the same throughout the office" (MPEP at page 700-8, column 1).

The foregoing definition of "reporter group", as used to support the claims in an issued patent, is consistent with that generally accepted in the relevant art, and applied in the present application. The generally recognized utility is "used in detection", and its utility in the present case for detection *inter alia* in chromatographic comparison between phosphoinositides is evident to those conversant with the art.

The present rejection cannot be maintained in the face of the foregoing evidence and Applicant therefore respectfully requests that it be withdrawn and the claims progressed to issue.

C. Rejection of Claim 83 Under 35 U.S.C. § 112, Second Paragraph

Former claim 83 in the '222 application, corresponding to claim 51 in the present application, is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention. Although Applicant respectfully traverses, these concerns are also addressed.

The Final Action at page 5 questions whether claim 83 is intended to define an admixture or simply each member of the "matched pair" in the alternative. Those of ordinary skill in the art would understand, from reading the present specification, that present claim 51 (counterpart to former claim 83) does not refer to admixtures. Indeed, the ordinary usage of the term "pairs" conveys such a meaning, which renders the claims sufficiently definite. *ZMI Corp. v. Cardiac Resuscitator Corp.*, 6 USPQ2d 1557 (Fed. Cir. 1988) (claim terms should be given their ordinary meaning, as would be understood by those of skill in the art, unless it is clear from the specification that the inventor intended to use such terms in a manner different to their accustomed meaning).

Such an ordinary meaning is further supported by the present specification, which, by way of example only, illustrates the comparative use in chromatography of each member of a matched pair of 2-modified and corresponding phosphoinositide without modification at 2- (specification on page 8, paragraph 2).

Nonetheless, and without acquiescing with the present rejection in any way, present claim 51 (counterpart to former claim 83) has been revised to further clarify that the matched

pairs comprise the 2-modified phosphatidylinositol-phosphate "and" the corresponding phosphatidylinositol-phosphate structure lacking the 2-modification.

In response to the foregoing reasoning, the Advisory Action further alleged that as certain precursor compounds may not be novel, the "matched pair" claims as a whole may lack novelty. In contrast, as the claims directed to matched pairs of compounds always require the presence of at least one of the novel and non-obvious compounds of the invention, as referenced in the earlier claims, the "matched pair" claims will always be patentable on this basis, irrespective of the status of the compound with which they are matched.

All § 112, second paragraph concerns are thus overcome and should be withdrawn.

D. <u>Prior Art Cited In Advisory Action</u>

The Advisory Action mailed in the '222 application alleges that certain of the present claims could read on the prior art, as exemplified by four new references included with the Advisory Action. Applicant respectfully traverses, and addresses these concerns by the following reasoning and the attached declaration.

It will first be noted that current claims 46 and 49, based upon former claims 86 and 89, have been revised to even further distance them from the prior art discussed and suggested in previous Official Actions. In particular, in the last line of part (b) of these claims, it is now stressed that R does not equal R′ when R = R′ = alkyl.

To the extent that prior art concerns were applied against former claim 81, these have now been even further addressed in current claim 52. In the allowed version of former claim 81, R^1 and R^2 were restricted to R = R′ = certain amino- and related functionalized and substituted alkyl and alkanoyl groups. Claims to other species, wherein R and R′ were defined as combinations of alkyl, alkenyl and certain amino- and related functionalized and substituted

alkyl and alkanoyl groups did not progress to allowance, primarily because the phrase "or where R = R′;" was alleged to read on prior art for 1,2-dialkanoyl or 1,2-dialkyl types with identical saturated alkyl groups attached in ester or ether linkage at the glycerol 1- and 2- positions. This concern is addressed herein.

The present specification at various places describes structural types wherein R^1 and R^2 are not identical, exemplified on page 6 paragraph 5 by 1-*O*-hexanoyl-2-*O*-(ω-Cbz-aminobutanoyl)-*sn*-glycero-3-phosphoric acid (**18,** Scheme II, FIG 2), on page 7 paragraph 2 by 1-*O*-hexanoyl-2-*O*-(aminobutanoyl)-*sn*-3-phosphatidyl-based PtdIns(4,5)P_2s, and the derived 4-azidosalicyl photoaffinity-labelled analogue, with corresponding examples on pages 16 and 17. With this support in the specification, new claim 52 is based on combinations of non-identical R^1 and R^2 for both the *myo*-inositol and the *scyllo*-inositol configurations of the 2-hydroxyl group. In this regard, it will be noted that the reference Thum *et al.*, 1996, cited in the Advisory Action, is not available as prior art against the new claim 52.

In fact, the following reasoning shows that none of the four references included with the Advisory Action are relevant to the presently claimed invention. The new references with the Advisory Action are a 1997 ACS reference to an original article by Thum *et al.*, published as *Tetrahedron Lett.*, 37(50):9017-9020, 1996; a 1996 ACS reference to an original article by Wang and Chen, published as *J. Org. Chem.*, 61(17):5905-5910, 1996; a 1996 ACS reference to an original article by Reddy *et al.*, published as *J. Org. Chem.*, 60(11): 3385-3390, 1995; and a 1995 ACS reference to an original article by Bruzik and Kubiak, published as *Tetrahedron Lett.*, 36(14): 2415-2418, 1995. None of these references constitute a bar to patentability of the presently claimed invention.

First, the references by Wang and Chen, Reddy *et al.* and Bruzik and Kubiak do not teach or suggest phosphoinositide analogues in accordance with the present invention, which are based on phosphatidylinositolphosphate, wherein the 2-OH is rendered non-nucleophilic by derivatization or replacement or wherein a reporter group or conjugand is incorporated in the fatty acyl or inositol residue.

Second, the Thum *et al.* and Wang and Chen references, irrespective of their content, are not available as prior art against the presently claimed invention. These references were published in December and August, 1996, respectively, and therefore do not constitute prior art against this application, which properly claims priority to a provisional application filed in June, 1996. Applicant takes the precaution of including a properly executed declaration under 37 C.F.R. § 1.131 to formally remove the Thum *et al.* and Wang and Chen references from consideration as prior art in the present application.

Accordingly, none of the four documents cited in the Advisory Action would form the basis of a proper prior art rejection against the presently claimed invention and any potential concerns under 35 U.S.C. §§ 102 or 103 are thus overcome.

VII. Formalities

The proper claim for priority is introduced into the specification by amendment and is reflected in the enclosed Inventor's Declaration. Formal drawings are enclosed herewith. Applicant's initial duty of disclosure is also met.

Should a Terminal Disclaimer be deemed necessary to secure allowance of the present claims, a telephone call to the Applicant's undersigned representative is solicited in order that the Disclaimer can be supplied without delay.

No fees should be due in addition to the enclosed filing fees. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Assistant Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4020.000499.

VIII. Conclusion

In conclusion, Applicant submits that, in light of the foregoing remarks, the present claims are in condition for allowance and an early indication to this effect is respectfully requested. Should Examiner Ambrose have any questions or comments, a telephone call to the undersigned Applicant's representative is earnestly solicited.

Respectfully submitted,

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